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Dated 10 February 2003

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11FEB02 E694617-2 D02029
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Request for grant of a patent

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The Patent Office

Cardiff Road
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1.	Your Reference	**AP/PI4749**
2.	Patent application number *(The Patent office will fill in this part)*	08 FEB 2002 **0203019.5**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**GLAXO GROUP LIMITED** **GLAXO WELLCOME HOUSE** **BERKELEY AVENUE** **GREENFORD** **MIDDLESEX** **UB6 ONN** **GB**
	Patents ADP number *(if you know it)*	06473587003
	If the applicant is a corporate body, give the country/state of its corporation	**GB**
4	Title of the invention	**CHEMICAL COMPOUNDS**
5	Name of your agent *(if you know one)*	**PETER I DOLTON**
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**GLAXOSMITHKLINE** **CORPORATE INTELLECTUAL PROPERTY** **CN925.1** **980 GREAT WEST ROAD** **BRENTFORD** **MIDDLESEX** **TW8 9GS, GB**
	Patents ADP number *(if you know it)*	08321846001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	**YES**

Patents Form 1/77

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Continuation sheets of this form	-
Description	21
Claim(s)	2
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature PETER I DOLTON. 8 February 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY
020 8047 4420

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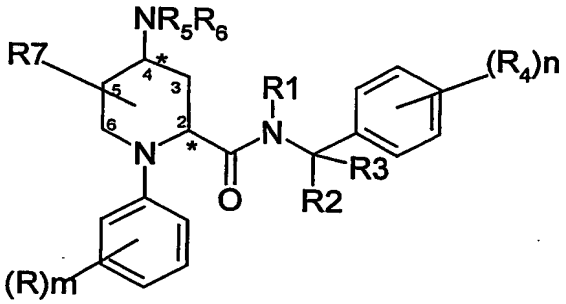
Chemical Compounds

The present invention relates to N-aryl piperidine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to novel compounds which are potent and specific antagonists of tachykinins, including substance P and other neurokinins.

Thus the present invention provides compounds of formula (I)



(I)

wherein

R represents halogen or C_{1-4} alkyl;

R_1 represents hydrogen, C_{1-4} alkyl;

R_2 represents hydrogen , C_{1-4} alkyl or R2 together with R_3 represents C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $C(O)NR_8R_9$, saturated 5 to 7 membered heterocyclic group, 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is a C_{1-6} alkyl group optionally substituted by one or two groups selected from fluorine, phenyl, hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl or R_5 and R_6 together with nitrogen to which they are attached represent a 5 to 7 membered heterocyclic group optionally containing another heroatom selected from O, N or S and optionally substituted by C_{1-4} alkyl or C(O) C_{1-4} alkyl.

R_7 represents hydrogen, halogen, C_{1-4} alkyl or $C(O)R_{10}$;

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl group;

R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

m is zero or an integer from 1 to 3;
n is an integer from 1 to 3;
and pharmaceutically acceptable salts and solvates thereof.

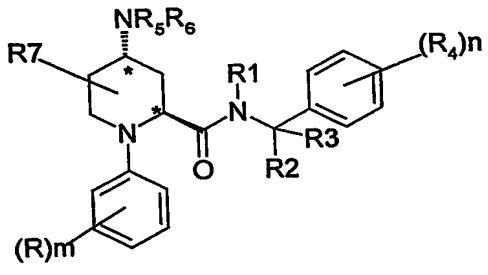
Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates.

The solvates may, for example, be hydrates.

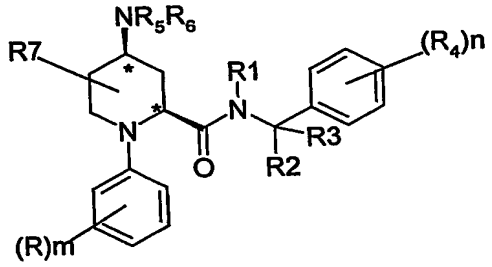
References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts together with pharmaceutically acceptable solvates.

Suitable pharmaceutical acceptable salts of the compounds of general formula (I) may be obtained in a crystalline form and/or in an amorphous form or as a mixture thereof.

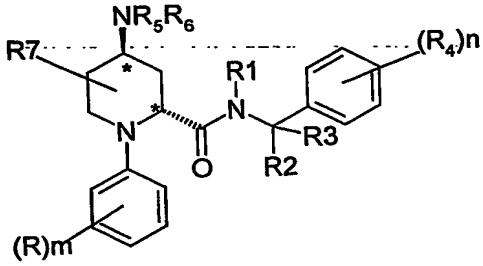
It will be appreciated by those skilled in the art that the compounds of formula (I) contain at least two chiral centres (namely the carbon atoms shown as * in formula (I)) and these may be represented by the formulae (1a, 1b, 1c and 1d).



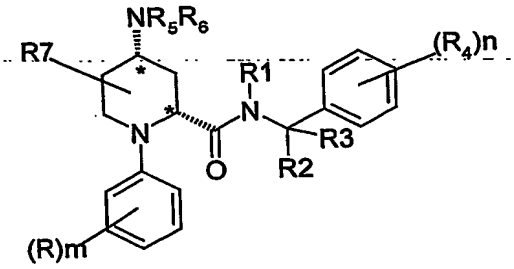
1a



1b



1c



1d

The wedge shaped bond indicates that the bond is above the plane of the paper and is referred to as β configuration. The broken bond indicates that the bond is below the plane of the paper and is in the α configuration.
The configuration of the chiral carbons atom of the piperidine ring shown in 1a and 1c is hereinafter referred to as anti configuration and in formulae 1b and 1d as the syn configuration.

Further asymmetric carbon atoms are possible in the compound of formula (I). Thus, for example, when R_2 and R_3 are not the same group, the compounds of formula (I) possess at least three asymmetric carbon atoms.

It is to be understood that all enantiomers and diastereoisomers and mixtures thereof are encompassed within the scope of the present invention.

The term C_{1-4} alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1 methylethyl or 2-methyl propyl.
The term C_{1-6} alkyl is meant to include C_{1-4}alkyl and the higher homologues thereof having 5 or 6 carbon atoms such as for example pentyl, 2-methylbutyl, hexyl, 2-methylpentyl or dimethylpropyl.

The term C $_{3-6}$ alkenyl group refers to a straight or branched alkenyl group containing from 3 to 6 carbon atoms; examples of such groups include 2-propenyl, 1 propenyl, isopropenyl, 2-butenyl, 2-pentenyl, 2-hexenyl and the like.

When R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group this group is saturated or contains a single double bond. This may be a 3,6-dihydro-2H-pyridin-1yl, a piperidin-1-yl or a pyrrolidin 1-yl group.

When R_5 is a 5 or 6 membered heteroaryl group according to the invention they include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridyl or pyrimidinyl.

When R_5 is saturated 5 to 7 membered heterocyclic group examples of this group include pirrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, 1.3 dioxolan-yl or morpholin-yl.

The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

A preferred group of compounds of formula (I) are those in which the substituents at the C-2 and C-4 positions of piperidine ring are in the syn configuration.

When R represents halogen this is suitably chlorine or more preferably fluorine or when R is C_{1-4} alkyl this is suitably methyl or ethyl wherein m is zero or an integer from 1 to 2.

Suitable values for R_2 or R_3 include hydrogen, a methyl, an ethyl or a propyl group.

R is preferably a halogen (e.g. fluorine) and/or a C_{1-4} alkyl (e.g. methyl) group and m is preferably zero or an integer from 1 to 2.

R_1 is preferably a methyl group.

R_2 is preferably a hydrogen atom or a methyl group.

R_3 is preferably a hydrogen atom or a methyl group.

R_4 is preferably a trifluoromethyl group or halogen (i.e chlorine).

A preferred class of compounds of formula (I) are those wherein each R is independently a halogen (e.g. fluorine) or a C_{1-4} alkyl (e.g. methyl) group, wherein m is 0, 1 or 2. More preferably m is 1 or 2. Within this class those wherein R is at the 2 and/or 4 position in the phenyl ring are particularly preferred.

Compounds of formula (I), wherein n is 2, represent a preferred class of compounds and within this class the groups R_4 are preferably at the 3 and 5 position in the phenyl ring.

Preferred compounds according to the invention are:
4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;
4-(4-Acetyl-piperazin-1-yl)-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
diasteroisomers and acceptable pharmaceutical salts thereof.

The compounds of the invention are antagonists of tachykinins, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.
The compounds of the present invention have also activity as serotonin reuptake inhibitors.

NK_1-receptor binding affinity has been determined in vitro by the compounds' ability to displace [3H] - substance P (SP) from recombinant human NK_1 receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.
CHO cell membranes were prepared by using a modification of the method described by Dam T and Quirion R (Peptides, 7:855-864, 1986). Thus ligand binding was performed in 0.4 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]Substance P (30÷56 Ci/mmol, Amersham), a final membrane concentration of 25 µg of protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min.. Non-specific binding was determined using excess of Substance P (1 µM) and represents about 6% of the total binding.
Compounds of the invention were further characterised in a functional assay for the determination of their inhibitory effect. Human-NK_1-CHO cells were stimulated with Substance P and the receptor activation was evaluated by measuring the accumulation of cytidinediphosphodiacylglycerol (CDP-DAG), which is the liponucleotide precursor of phosphatidylinositol diphosphate. CDP-DAG accumulates in the presence of Li^+ as a consequence of the receptor mediated activation of phospholipase C (PLC) (Godfrey, Biochem. J., 258:621-624, 1989). The method is described in detail by Ferraguti et al. (Mol. Cell. Neurosci., 5:269-276, 1994).

The action of the compounds of the invention at the NK_1 receptor may be determined by using conventional tests. Thus the ability to penetrate the central nervous system and to bind at the NK_1 receptor was demonstrated in vivo by their inhibitory effect on the change in the behaviour induced by intracerebroventricular applied substance P in the gerbil, according to the gerbil foot tapping model as described by Rupniak & Williams, Eur. J. of Pharmacol., 1994,.
Human Serotonin Transporter (hSERT) binding affinity has been determined in vitro by the compounds' ability to displace [^{3}H]- Imipramine from human serotonin transporter expressed in Human Embryonic Kidney HEK293 cell membranes (Receptor Biology Inc.). For the binding reaction, 4 nM of [^{3}H]- Imipramine (703 GBq/mmol, Amersham) were incubated with 0.02 mg/ml of cell membrane and the compound to be tested at different concentrations (7 concentration points) in 50 mM Tris HCl, pH 7.5, 120 mM of NaCl and 5 mM KCl. The reaction was performed for 60 min at 4°C and was terminated by filtration through GF/B

Unifilters 96 wells/case (presoaked in 0.5 % PEI) using a Cell Harvester (Packard). Scintillation fluid was added to each filtered spot and radioactivity was determined using a scintillation counter (TopCount (Packard)). Non-specific binding was determined using Imipramine (100μM) and represents about 5% of the total binding.

Competition experiments were conducted with duplicate determination for each point.

Msat601 software package was used to elaborate the competition binding data.

IC_{50} values were converted to K_i values using Cheng-Prusoff equation.

Compounds of the invention are useful in the treatment of CNS disorders. In particular they are useful in the treatment or prevention of major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, the treatment of anxiety and the treatment of panic disorders. Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

Compounds of the invention have also been found to exhibit anxiolytic activity in conventional tests. For example in marmoset human threat test (Costall et al., 1988).

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis;

migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.

Compounds of the invention are of particular use in the treatment of depressive states, in the treatment of anxiety and of panic disorders.
Depressive states include major depressive disorders including bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, dysthymic disorder with early or late onset and with or without atypical features, neurotic depression and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type.

Compounds of the invention may be administered in combination with other active substances such as 5HT3 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron and metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine and metoclopramide.

Suitable SSRI which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline and zimeldine.

Suitable SNRI which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations) or sequentially.

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms. Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable

excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

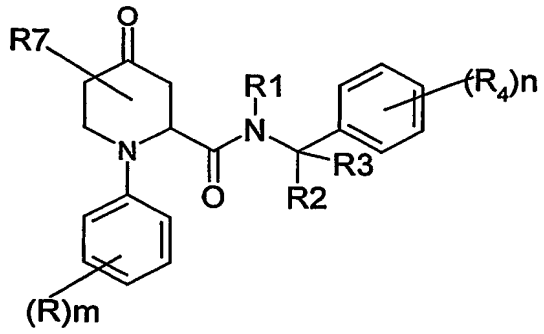
The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1, R_2, R_3, R_4, R_5 R_6 R_7 R_8 R_9 or R_{10} m and n , have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by reductive N-alkylation of a compound of formula (II),



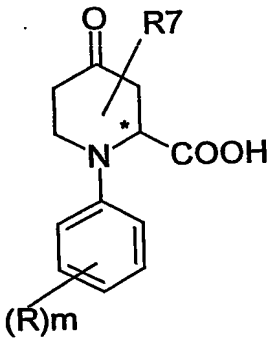
(II)

NR_5R_6

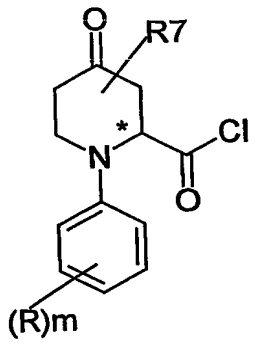
(III)

with an amine derivative (III) in an aprotic solvent such as dichloroethane and in the presence of a suitable metal reducing agent such as sodium borohydride or sodium triacetoxyborohydride.

Compounds of formula (II) may be prepared by treating compounds of formula (IV)

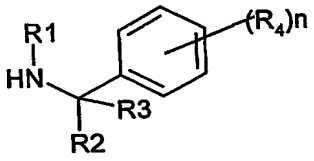


(IV)



(V)

with thionyl chloride in an aprotic solvent such as dichloromethane and in the presence of an organic base such triethylamine to form the intermediate carbonyl chloride compound (V) which may be isolated if required, followed by reaction of compound (V) with the amine compound (VI)



(VI)

The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon, a halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran optionally in the presence of a base such as a tertiary amine e.g. diisopropylethylamine.

Alternatively compound of formula (II) may be prepared by reaction of compound (IV) with with an amine (VI) in the presence of condensing agents such as O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate, in a convenient solvent such as DMF.

Where it is desired to isolate a compound formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether or tetrahydrofuran).

Pharmaceutically acceptable salts may also be prepared from other salts, including other pharmaceutically acceptable salts, of the compounds of formula (I) using conventional methods.

Compounds of formula , (IV), (V) and (VI) may be prepared by analogous methods to those used for known compounds.

The compounds of formula (I) may readily be isolated in association with solvent molecules by crystallisation from or evaporation of an appropriate solvent to give the corresponding solvates.

When a specific enantiomer of a compound of general formula (I) is required, this may be obtained for example by resolution of a corresponding enantiomeric mixture of a compound of formula (I) using conventional methods.
Thus, for example, specific enantiomers of the compounds of formula (I) may be obtained from the corresponding enantiomeric mixture of a compound of formula (I) using chiral HPLC procedure.

Alternatively, enantiomers of a compound of general formula (I) may be synthesised from the appropriate optically active intermediates using any of the general processes described herein.

Thus for example the required enantiomer may be prepared by the corresponding a chiral piperidin-4-one of formula (IV) using the process described above for preparing compounds of formula (I) from compounds (IV), followed by separation of the diastereomeric mixture of a compound of formula (I) using conventional procedure.

The chiral compounds (IV) may be prepared from the corresponding racemic compound (IV) using conventional procedures such as salt formation with a suitable optically active acid, separating the resultant diastereoisomeric salts by conventional means e.g. chromatography and crystallisation followed by hydrolysis of the diastereoisomeric salts.

In a further embodiment of the invention the enantiomers of the compound of formula (I) may be prepared by reaction of a chiral amine (VI) using any of the processes described above for preparing compounds of formula (I) from amine (V).
The chiral amine (III) may be prepared from the corresponding racemic amine (III) using any conventional procedures such as salt formation with a suitable optically active acid.

The invention is further illustrated by the following Intermediates and Examples which are not intended as a limitation of the invention.
In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Buchi m.p. apparatus and are uncorrected. R.T. or r.t. refer to room temperature.
Infrared spectra (IR) were measures in chloroform or nujol solutions on a FT-IR instrument.
Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 400 or

500 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were taken on a VG Quattro mass spectrometer. Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 mL, λ = 589 nm). Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany. T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. Solutions were dried over anhydrous sodium sulphate.
Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.
The following abbreviation are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-dimethylformamide, Et2O = diethyl ether, EtOH = ethanol, MeOH = methanol, TEA = triethylamine, THF = tetrahydrofuran.

Intermediate 1
(4-Fluoro-2-methyl-phenylimino)-acetic acid, ethyl ester
A solution of ethyl glyoxalate (50% solution in toluene – 40.8 mL) in toluene (180 mL) was heated to reflux for 1.5 hours under a Nitrogen atmosphere, in a flask equipped with a Dean Stark apparatus. Then, a solution of 4-fluoro-2-methyl-aniline (10 g) in dry toluene (20 mL) was slowly added. The mixture was heated to reflux for 3 hours, then it was concentrated *in vacuo*. The residue was purified by flash chromatography (toluene/CH/AcOEt 4:4:2) to give the title compound (13.06 g) as a yellow oil.
T.l.c.: toluene/CH/AcOEt 4:4:2, Rf=0.67.
NMR (CDCl3): δ (ppm) 7.8 (s, 1H); 6.95 (d, 1H); 6.85 (d, 2H); 4.4 (q, 2H); 2.35 (s, 3H); 3.3 (t 3H).
MS (ES/+): m/z=210 $[M+H]^+$.

Intermediate 2
1-(4-Fluoro-2-methyl-phenyl)-4-oxo-1,2,3,4-tetrahydro-pyridine-2-carboxylic acid, ethyl ester
Boron trifluoride etherate (1.22 mL) was added to a solution of intermediate 1 (2 g) in anhydrous DCM (20 mL) previously cooled to –78°C under a Nitrogen atmosphere. After stirring for 15 minutes at –78°C, the 1-methoxy-3-trimethylsiloxy-1,3-butadiene (2.67 mL) was dropped over 45 minutes. The resulting solution was stirred at –78°C for 2 hours, then TFA (0.74 mL) was added. The mixture was stirred at 0°C for 15 minutes, next a saturated sodium hydrogen carbonate solution was added and the mixture was extracted with AcOEt (3 x 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a residue, which was purified by flash chromatography (CH/AcOEt from 8:3 to 7:3) to give the title compound (1.5 g) as a pale yellow solid.
T.l.c.: CH/AcOEt 6:4, Rf=0.2.

NMR (CDCl3): δ (ppm) 7.4 (dd, 1H); 7.1 (d, 1H); 7.0-6.8 (m, 2H); 5.15 (d, 1H); 4.4 (m, 1H); 4.1 (m, 2H); 3.1-2.85 (m, 2H); 2.4 (s, 3H); 1.15 (t, 3H).

Intermediate 3

1-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, ethyl ester

L-selectride (1M solution in dry THF, 3.96 mL) was added drop-wise, over 1 hour, to a solution of intermediate **2** (1 g) in dry THF (30 mL) previously cooled to -78°C under a Nitrogen atmosphere. After 1 hour, a saturated sodium hydrogen carbonate solution (20 mL) was added drop-wise and the solution was extracted with AcOEt (3 x 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (810 mg) as a white solid.
T.l.c.: CH/AcOEt 6:4, Rf=0.6.
NMR (CDCl3): δ (ppm) 7.4 (dd, 1H); 7.1 (dd, 1H); 6.9 (dd, 1H); 6.8 (dt, 1H); 4.2 (q, 2H); 4.15 (m, 1H); 3.6 (m, 1H); 3.2 (m, 1H); 2.8-2.7 (dd, 2H); 2.6 (m, 2H); 2.4 (s, 3H); 1.2 (t, 3H).

Intermediate 4

1-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid

Lithium hydroxide monohydrate (241 mg) was added to a solution of intermediate**3** (300 mg) in MeOH (15 mL) and water (3 mL) and the resulting solution was stirred at 80°C for 1 hour. The solution was allowed to cool to r.t. and extracted with Et2O. The aqueous layer was acidified until pH=6 with acetic acid and extracted with AcOEt (3 x 15 mL). The combined organic extractes were dried and concentrated *in vacuo* to give the title compound (230 mg) as yellow solid, which was used without any further purification in the next step.
MS (ES/+): m/z=252 $[M+H]^+$.

Intermediate 5

1-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid,

DIPEA (0.47 mL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (385.3 mg) were added to a solution of intermediate **4** (230 mg) in anhydrous DMF (20 mL) under a Nitrogen atmosphere. After stirring for 15 minutes, (3,5-dichlorobenzyl)-methylamine hydrochloride (225 mg) was added and the mixture was stirred at r.t. for 4 hours. The solution was diluted with water (30 mL) and extracted with AcOEt (3 x 60 mL). The combined organic extracts were washed with cold water (50 mL) and brine (3 x 80 mL), then concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (176 mg) as a pale yellow solid.
T.l.c.: CH/AcOEt 3:7, Rf=0.52.
NMR (d_6-DMSO): δ (ppm) 7.5-7.45 (2t, 1H); 7.14-6.88 (2d, 2H); 7.05 (dd, 1H); 6.92 (dd, 1H); 6.82 (dt, 1H); 4.66-4.51 (2m, 1H); 4.59 (d, 1H); 4.15 –4.1 (d+m, 1H); 3.83-3.57 (2m, 1H); 3.05 (m, 1H); 2.73 (m, 1H); 2.51 (m, 1H); 2.4-2.25 (m, 2H); 2.66-2.37 (2s, 3H); 2.37-2.24 (2s, 3H).
MS (ES/+): m/z=423 $[M+H]^+$.

Intermediate 6
1-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (6a diatereoisomer 1) 1-(4-Fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (6b diastereoisomer 2)

DIPEA (0.531 mL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (423 mg) were added to a solution of intermediate 4 (298 mg) in anhydrous DMF (15 mL) under a Nitrogen atmosphere and the resulting solution was stirred at r..t for 15 minutes.

At the same time, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine maleate (500 mg) was treated with a saturated sodium hydrogen carbonate solution (10mL) and extraction with AcOEt (2 x 30 mL); the organic layer was dried and concentrated *in vacuo* to give [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamine (303 mg). This intermediate was added to the previous solution and the mixture was stirred at 23°C for 36 hours.

The solution was diluted with water (30 mL) and extracted with AcOEt (3 x 60 mL). The combined organic extracts were washed with cold water (2 x 50 mL) and brine (2 x 50 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 1:1) to give:

1. intermediate **6a** (56 mg) as yellow oil.
2. intermediate **6b** (36 mg) as yellow oil.

Intermediate 6a

T.l.c.: CH/AcOEt 1:1, Rf=0.6.

NMR (d_6-DMSO): δ (ppm) 7.95 (s, 1H); 7.72 (s, 2H); 7.02 (m, 2H); 6.94 (m, 1H); 5.71 (q, 1H); 4.62 (m, 1H); 3.55 (m, 1H); 3.01 (m, 1H); 2.67 (m, 1H); 2.34-2.17 (m, 4H); 2.04 (s, 3H); 1.33 (d, 3H).

Intermediate 6b

T.l.c.: CH/AcOEt 1:1, Rf=0.4.

NMR (d_6-DMSO): δ (ppm) 8.02 (bs, 1H); 7.76 (bs, 2H); 6.95 (dd, 1H); 6.69 (dt, 1H); 6.46 (dt, 1H); 5.76 (q, 1H); 4.56 (m, 1H); 3.52 (m, 1H); 3.0 (m, 1H); 2.68 (m, 1H); 2.44 (m, 1H); 2.26 (m, 5H); 2.15 (s, 3H); 1.4 (d, 3H).

Example 1
4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide (1a anti isomer)
4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide (1b syn isomer)

Cyclopropylamine (0.012 mL) and sodium triacetoxyborohydride (38.1 mg) were added to a solution of intermediate **5** (50 mg) in anhydrous acetonitrile (3 mL) under a Nitrogen atmosphere. The solution was stirred at r.t. for 2 hours, then further cyclopropylamine (0.006 mL) and sodium triacetoxyborohydride (25.4 mg) were added. The mixture was stirred at 23°C for 2 days. The solution was diluted with AcOEt (15 mL) and washed with a 5% sodium hydrogen carbonate solution (15 mL) and brine (10 mL). The organic layer was dried

and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 85:15) to give two fractions:

1. example **1a** (8.5 mg) as colourless oil
2. example **1b** (10.1 mg) as colourless oil.

Example 1a

T.l.c.:AcOEt/MeOH 85:15, Rf=0.23.

NMR (d_6-DMSO): δ (ppm) 7.36 (bs, 1H); 7.12 (dd, 1H); 6.95 (bs, 2H); 6.89 (bd, 1H); 6.82 (bt, 1H); 4.48 (d, 1H); 4.32 (bm, 1H); 4.31 (bm, 1H); 3.48 (bm, 1H); 3.1 (bm, 1H); 2.83 (m, 3H); 2.78 (bm, 1H); 2.24 (s, 3H); 2.12 (m, 1H); 1.94 (m, 2H); 1.77 (m, 1H); 1.53 (m, 1H); 0.4 (m, 2H); 0.26 (m, 2H).

MS (ES/+) m/z=464 $[M+H]^+$.

Example 1b:

T.l.c.:AcOEt/MeOH 85:15, Rf=0.18.

NMR (d_6-DMSO): δ (ppm) 7.33 (bs, 1H); 7.11 (bm, 1H); 6.91 (bd, 2H); 6.85 (bs, 1H); 6.82 (bm, 1H); 4.4 (bm, 1H); 4.2 (bm, 1H); 4.15 (bd, 1H); 3.03 (bm, 1H); 2.96 (bs, 3H); 2.75 (bt, 1H); 2.5 (bm, 1H); 2.28 (bs, 3H); 2.11 (bm, 2H); 1.91 (bm, 1H); 1.53 (bq, 1H); 1.47 (bq, 1H); 0.39 (m, 2H); 0.23 (m, 2H).

MS (ES/+) m/z=464 $[M+H]^+$.

Example 2

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid,(3,5-dichloro-benzyl)-methylamide hydrochloride (anti isomer)

A solution of example **1a** (8 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 0.019 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 3 mL) to give the title compound as a white solid (6.6 mg).

NMR (d_6-DMSO – 70°C): δ (ppm) 8.93 (bs, 2H); 7.42 (s, 1H); 7.2-6.8 (bm, 5H); 4.7-3.4 (m, 5H); 3.0-2.6 (m, 5H); 2.3-2.0 (m, 6H); 1.76 (m, 1H); 1.0-0.8 (m, 4H).

MS (ES/+) m/z=464 $[M+H-HCl]^+$.

Example 3

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid,(3,5-dichloro-benzyl)-methylamide hydrochloride (syn isomer)

A solution of example **1b** (9 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 0.021 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 3 mL) to give the title compound as a white solid (9.3 mg).

NMR (d_6-DMSO – 70°C): δ (ppm) 9.0 (bs, 2H); 7.36 (s, 1H); 7.15 (bt, 1H); 6.95 (dd, 1H); 6.85 (m, 1H); 6.83 (s, 2H); 4.3 (bd, 1H); 4.8-4.0 (bm, 2H); 3.45 (bm, 1H); 3.0 (m, 1H); 2.8-2.5 (m, 2H); 3.04 (s, 3H); 2.31 (s, 3H); 2.3 (bm, 1H); 2.13 (bd, 1H); 1.92 (q, 1H); 1.82 (dq, 1H); 0.92-0.8 (m, 4H).

MS (ES/+) m/z=464 $[M+H-HCl]^+$.

Example 4

4-(4-Acetyl-piperazin-1-yl)-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide (4a anti isomer)

4-(4-Acetyl-piperazin-1-yl)-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid,(3,5-dichloro-benzyl)-methylamide(4b syn isomer) Acetyl-piperazine (35.8 mg) and sodium triacetoxyborohydride (58.1 mg) were added to a solution of intermediate 5 (58 mg) in anhydrous acetonitrile (3 mL) under a Nitrogen atmosphere. The solution was stirred at r.t. for 24 hours, then it was diluted with AcOEt (15 mL) and washed with a 5% sodium hydrogen carbonate solution (15 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 85:15) to give two fractions:

1. example **4a** (2 mg) as colourless oil
2. example **4b** (9 mg) as colourless oil.

Example 4a

T.l.c.:AcOEt/MeOH 8:2, Rf=0.33.

Example 4b:

T.l.c.:AcOEt/MeOH 8:2, Rf=0.23.

NMR (d_6-DMSO): δ (ppm) 7.33 (s, 1H); 7.09 (m, 1H); 6.92-6.79 (m, 4H); 4.5-4.2 (bm, 2H); 4.16 (d, 1H); 3.43 (m, 4H); 3.04 (m, 2H); 2.9 (bs, 3H); 2.5 (m, 5H); 2.29 (bs, 3H); 2.11-1.6 (m, 4H); 1.26 (s, 3H).

MS (ES/+) m/z=535 $[M+H]^+$.

Example 5

4-(4-Acetyl-piperazin-1-yl)-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide hydrochloride (syn isomer)

A solution of example **4b** (5.3 mg) in dry Et2O (1 mL) was treated with hydrochloric acid (1M in Et2O – 0.011 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 3 mL) to give the title compound as a white solid (4.5 mg).

MS (ES/+) m/z=535 $[M+H-HCl]^+$.

Example 6

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (6a anti isomer)

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (6b syn isomer)

Cyclopropylamine (0.015 mL) was added to a solution of intermediate **6a** (56 mg) in anhydrous acetonitrile (1 mL) under a Nitrogen atmosphere. The solution was stirred at r.t. for 10 minutes, then sodium triacetoxyborohydride (34 mg) was added. The mixture was stirred at 23°C for 18 hours, then it was diluted with DCM (15 mL) and washed with a 5% sodium hydrogen carbonate solution (15 mL) and brine (10 mL). The organic layer was dried

and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 9:1) to give two fractions:

1. example **6a** (12 mg) as yellow oil
2. example **6b** (23 mg) as yellow oil.

Example 6a:

T.l.c.: AcOEt/MeOH 9:1, Rf=0.32.

HPLC: column: Supelcosil ABZ Plus 15cm x 46mm x 5µ; mobile phase: acetonitrile/10mM ammonium acetate solution from 40:60 to 90:10 in 5 minutes, then 90:10 for 10 minutes; flux = 0.8 mL/min; λ=360nm; retention time 10.2 minutes.

Example 6b:

T.l.c.: AcOEt/MeOH 9:1, Rf=0.22.

HPLC: column: Supelcosil ABZ Plus 15cm x 46mm x 5µ; mobile phase: acetonitrile/10mM ammonium acetate solution from 40:60 to 90:10 in 5 minutes, then 90:10 for 10 minutes; flux = 0.8 mL/min; λ=360nm; retention time 9.4 minutes.

Example 7

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride (anti isomer)

A solution of example **6a** (12 mg) in dry Et2O (0.5 mL) was treated with hydrochloric acid (1M in Et2O – 0.024 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound as a yellow solid (7.7 mg).

NMR (d_6-DMSO): δ (ppm) 8.9 (bm, 1H); 8.0-7.96 (2s, 1H); 7.78-7.41 (2s, 2H); 7.4-6.65 (m, 3H); 5.73-5.32 (2q, 1H); 4.5-4.46 (2m, 1H); 4.2-4.16 (2bm, 1H); 3.5-2.4 (bm + m, 3H); 2.53-2.29 (2s, 3H); 2.29-2.03 (2s, 3H); 2.17 (m, 2H); 2.0 (m, 1H); 1.7 (m, 1H); 1.57-1.33 (2d, 3H); 0.87 (m, 2H); 0.78 (m, 2H).

MS (ES/+) m/z=547[M+H-HCl]$^+$.

Example 8

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride(syn isomer)

A solution of example **6b** (22 mg) in dry Et2O (0.5 mL) was treated with hydrochloric acid (1M in Et2O – 0.044 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound as a yellow solid (18 mg).

NMR (d_6-DMSO): δ (ppm) 9.0 (bm, 2H); 7.9 (bs, 1H); 7.63 (bs, 2H); 7.13 (m, 1H); 6.94 (m, 1H); 6.86 (bm, 1H); 5.56 (bq, 1H); 4.25 (bd, 1H); 3.7-2.4 (bm + bm + bm, 4H); 2.85 (bs, 3H); 2.28 (bs, 3H); 2.27 (bm, 1H); 2.14 (bm, 1H); 1.96 (m, 1H); 1.84 (m, 1H); 1.28 (bd, 3H); 0.91 (m, 2H); 0.82 (m, 2H).

MS (ES/+) m/z=547[M+H-HCl]$^+$.

Example 9

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (9a anti isomer) 4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide (9b syn isomer)

Cyclopropylamine (0.010 mL) was added to a solution of intermediate **6b** (36 mg) in anhydrous acetonitrile (1 mL) under a Nitrogen atmosphere. The solution was stirred at r.t. for 10 minutes, then sodium triacetoxyborohydride (22 mg) was added. The mixture was stirred at 23°C for 18 hours, then it was diluted with DCM (15 mL) and washed with a 5% sodium hydrogen carbonate solution (15 mL) and brine (10 mL). The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (AcOEt/MeOH 9:1) to give:

1. example **9a** (3.7 mg) as yellow oil
2. example **9b** (2.7 mg) as yellow oil.

Example 9a:

T.l.c.: AcOEt/MeOH 9:1, Rf=0.43.

HPLC: column: Supelcosil ABZ Plus 15cm x 46mm x 5μ; mobile phase: acetonitrile/10mM ammonium acetate solution from 40:60 to 90:10 in 5 minutes, then 90:10 for 10 minutes; flux = 0.8 mL/min; λ=360nm; retention time 10.2 minutes.

Example 9b:

T.l.c.: AcOEt/MeOH 9:1, Rf=0.31.

HPLC: column: Supelcosil ABZ Plus 15cm x 46mm x 5μ; mobile phase: acetonitrile/10mM ammonium acetate solution from 40:60 to 90:10 in 5 minutes, then 90:10 for 10 minutes; flux = 0.8 mL/min; λ=360nm; retention time 8.99 minutes.

Example 10

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride

A solution of example **9a** (3.7 mg) in dry Et2O (0.5 mL) was treated with hydrochloric acid (1M in Et2O – 0.0074 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound as a yellow solid (2.1 mg).

NMR (d_6-DMSO): δ (ppm) 8.8 (bm, 1H); 8.71 (bm, 1H); 8.04 (bs, 1H); 7.73 (bs, 2H); 6.95 (m, 2H); 6.65 (dt, 1H); 5.84 (q, 1H); 4.45 (m, 1H); 3.98 (bm, 1H); 3.59 (m, 1H); 2.91 (m, 1H); 2.78 (m, 1H); 2.39 (s, 3H); 2.18 (s, 3H); 2.2 (bm, 1H); 2.09 (m, 1H); 2.0 (m, 1H); 1.63 (m, 1H); 1.47 (d, 3H); 0.83 (m, 4H).

MS (ES/+) m/z=547[M+H-HCl]$^+$.

Example 11

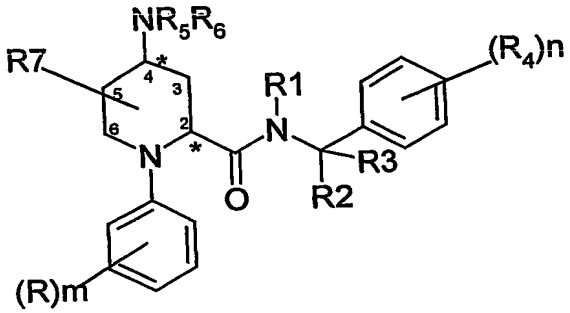
4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid,[1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide hydrochloride

A solution of example **9b** (2.7 mg) in dry Et2O (0.5 mL) was treated with hydrochloric acid (1M in Et2O – 0.0054 mL) at 0°C under a Nitrogen atmosphere. The resulting solution was

stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound as a yellow solid (2.0 mg).
NMR (d_6-DMSO): δ (ppm) 8.81 (bs, 2H); 7.89 (bs, 1H); 7.52 (bs, 2H); 7.09 (m, 1H); 6.89 (bd, 1H); 6.71 (bm, 1H); 5.62 (bq, 1H); 4.29 (bd, 1H); 3.45 (bm 1H); 3.0 (bd, 1H); 2.9-2.4 (bm, 2H); 2.85 (s, 3H); 2.29 (s, 3H); 2.29 (bm, 1H); 2.13 (m, 1H); 1.88 (bq, 1H); 1.79 (m, 1H); 1.38 (bd, 3H); 0.85 (m, 4H).
MS (ES/+) m/z=547$[M+H-HCl]^+$.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims



(I)

wherein

R represents halogen or C_{1-4} alkyl;

R_1 represents hydrogen, C_{1-4} alkyl;

R_2 represents hydrogen , C_{1-4} alkyl or R2 together with R_3 represents C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents rifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $C(O)NR_8R_9$, saturated 5 to 7 membered heterocyclic group, 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is a C_{1-6} alkyl group optionally substituted by one or two groups selected from fluorine, phenyl, hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl or R_5 and R_6 together with nitrogen to which they are attached represent a 5 to 7 membered heterocyclic group optionally containing another heroatom selected from O, N or S and optionally substituted by C_{1-4} alkyl or C(O) C_{1-4} alkyl.

R_7 represents hydrogen, halogen, C_{1-4} alkyl or $C(O)R_{10}$;

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl group;

R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 3;

and pharmaceutically acceptable salts and solvates thereof..

2. A compound selected from:

4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;

4-(4-Acetyl-piperazin-1-yl)-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;
4-Cyclopropylamino-1-(4-fluoro-2-methyl-phenyl)-4-oxo-piperidine-2-carboxylic acid, [1-(R)-3,5-bis-trifluoromethyl-phenyl)-ethyl]-methylamide;
diasteroisomers and acceptable pharmaceutical salts thereof.

3. A compound as claimed in claim 1 or 2 for use in therapy.

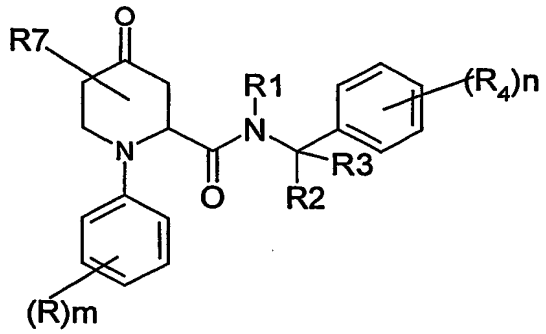
4. The use of a compound as claimed in claim 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

5. The use of a compound as claimed in claim 1 or 2 for use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins

6. A pharmaceutical composition comprising a compound as claimed in claim 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins, comprising administration of an effective amount of a compound as claimed in claim 1 or 2.

8. A process for the preparation of a compound as claimed in claim 1 or 2, which comprises reacting a compound of formula (II),



(II)

NR_5R_6 (III)

with amine (III) in the presence of a suitable metal reducing agent, followed where necessary or desired by one or more of the following steps

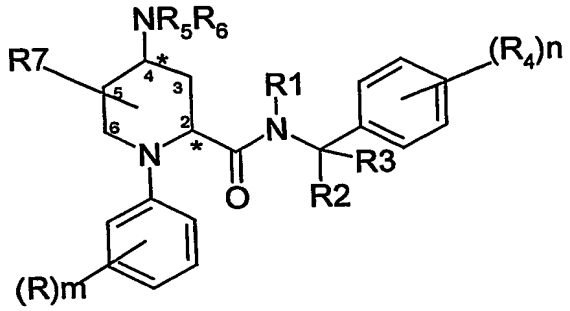
i) removal of any protecting group;

ii) isolation of the compound as a salt or a solvate thereof;

iii) separation of a compound of formula (I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to amine derivatives of formula (I)



(I)

wherein

R represents halogen or C_{1-4} alkyl;

R_1 represents hydrogen, C_{1-4} alkyl;

R_2 represents hydrogen , C_{1-4} alkyl or R2 together with R_3 represents C_{3-7} cycloalkyl;

R_3 represents hydrogen, C_{1-4} alkyl, C_{3-7} cycloalkyl or C_{3-6} alkenyl; or R_1 and R_3 together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group;

R_4 represents rifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_5 represents hydrogen, phenyl, C_{3-7} cycloalkyl, $C(O)NR_8R_9$, saturated 5 to 7 membered heterocyclic group, 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or R_5 represents a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms, or R_5 is a C_{1-6} alkyl group optionally substituted by one or two groups selected from fluorine, phenyl, hydroxy, amino, dimethylamino, aminocarbonyl, C_{1-4} alkoxy or trifluoromethyl;

R_6 represents hydrogen or C_{1-4} alkyl or R_5 and R_6 together with nitrogen to which they are attached represent a 5 to 7 membered heterocyclic group optionally containing another heroatom selected from O, N or S and optionally substituted by C_{1-4} alkyl or C(O) C_{1-4} alkyl.

R_7 represents hydrogen, halogen, C_{1-4} alkyl or $C(O)R_{10}$;

R_8 and R_9 are independently hydrogen or C_{1-4} alkyl group;

R_{10} represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to 3 nitrogen atoms;

m is zero or an integer from 1 to 3;

n is an integer from 1 to 3;

and pharmaceutically acceptable salts and solvates thereof, the process for their preparation and their use in the treatment of condition mediated by tachykinins.